UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,769	06/27/2006	Sam Philip Heywood	CELL-0308	7843

20306 7590 09/30/2008

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
09/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,769	HEYWOOD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-7,14,15,17-38,41 and 43* is/are pending in the application.

4a) Of the above claim(s) *21-23 and 30-38* is/are withdrawn from consideration.

5)☒ Claim(s) *5-7* is/are allowed.

6)☒ Claim(s) *4, 14-15, 17-20, 24-29, 41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-3, 8-13, 16, 39-40, 42 and 44 are cancelled.
Claims 4, 14,-15, 17-20, 24, 27, 41 and 43 have been amended.

2. Claims 21-23 and 30-38 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 4-7, 14-15, 17-20, 24-29, 41 and 43 are under consideration.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the first line of the specification as not containing a priority claim is withdrawn in view of the amendments to the specification filed 6/26/08 and applicants' remarks.

6. The objection to claim 43 in the recitation "claims 1 or 24" is withdrawn in view of the amendments to the claim.

7. The rejection of claims 15-16 under 35 U.S.C. 112, second paragraph, as being indefinite in reciting that both the cysteine in the light chain constant region and the cysteine in the heavy chain constant region are attached to an effector molecule is withdrawn in view of the amendments to claim 15 and the cancellation of claim 16.

8. The rejection of claims 15-16 and 20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendments to the claims.

9. The rejection of claims 1-3, 8-15, 17-18, 39-40 and 42-44 under 35 U.S.C. 102(b) as being anticipated by Carter P. J. (WO 93/06217, 4/1/1993) as evidenced by Bodmer et al (WO 89/01974) is withdrawn in view of the amendments to the claims and the cancellation of claims 1-3, 8-13, 39, 40, 42 and 44.

10. The rejection of claims 1-2, 4, 8-13, 39-40, 42 and 44 under 35 U.S.C. 102(b) as being anticipated by Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed

10/20/06) is withdrawn in view of the amendments to the claims and the cancellation of claims 1-3, 8-13, 39-40, 42 and 44.

11. The rejection of claims 1-3 under 35 U.S.C. 103(a) as being unpatentable over Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) in view of Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06) is withdrawn in view of the cancellation of the claims.

12. The rejection of claims 1-2, 8-13, 39-40, 42 and 44 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) is withdrawn in view of the cancellation of the claims.

Rejections Maintained and New Grounds of Rejections

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. The rejection of claims 24-29 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 6/26/2008 states that the amendments to the claims are sufficient to overcome the written description rejection. Applicant directs the examiners attention to pg. 12 and Example 1 where reductants are discussed. Applicants' arguments have been fully considered but are not found persuasive. Claims 24-29 still encompass a genus antibody fragments comprising a Fab or Fab' wherein the interchain cysteines of the heavy and light chains are not substituted and wherein each

of the interchain cysteines are attached to an effector molecule and the heavy and/or light chain further comprises an additional cysteine attached to an effector molecule. Thus, the amendments to the claims are insufficient to overcome the instant rejection. The description at pg. 12 of the specification and Example 1 is acknowledged, however, while pg. 12 generally discloses that a reducing agent can be used to remove the covalent linkage between the CH1 and CL interchain cysteines, Example 1 discloses the reduction of the g165 Fab' using different reductants and the attachment of PEG molecules to the fragments as determined by size exclusion HPLC (Figure 1). However, the disclosure that thiol based reduction typically resulted in monoPEGylated Fab' because the reductants were not strong enough to reduce the inter-chain disulfide bond and the attachment of two or more PEG molecules when the inter-chain disulfide linkage between the heavy and light chain was removed by replacing either the interchain cysteine of CL or the interchain cysteine of CH1 with serine does not adequately describe the genus of antibody fragments comprising a Fab or Fab' wherein each interchain cysteine of the CH1 and CL regions are attached to an effector molecule. Clearly, one of skill in the art would not recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus.

For these reasons and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. The rejection of claim 4 under 35 U.S.C. 102(b) as being anticipated by Carter P. J. (WO 93/06217, 4/1/1993) as evidenced by Bodmer et al (WO 89/01974) is maintained.

The response filed 6/26/08 states that claim 4 has been amended to recite that then hinge region of the claimed antibody fragment is modified to comprise SEQ ID NO:1 or SEQ ID NO:2, which is not found in the Carter or Bodmer references. This has been fully considered but is not found persuasive. Carter teaches that the Fab' may include a hinge region, a modified hinge having more than one cysteinyl residue or a naturally occurring hinge region such as human IgG1 (necessarily comprises SEQ ID NO:1 as evidenced by Bodmer et al, see Fig. 1). Thus, the naturally occurring hinge region of IgG1 as taught by Carter necessarily comprises the sequence of SEQ ID NO:1. Applicant is reminded that the transitional term "comprising" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., *Mars Inc. v. H.J. Heinz Co.*, 377 F.3d 1369, 1376, 71 USPQ2d 1837, 1843 (Fed. Cir. 2004) (MPEP 2111.03).

Thus, Carter et al anticipates the claim as evidenced by Bodmer and the rejection is maintained.

17. The rejection of claims 14-15, 17-19, 41 and 43 under 35 U.S.C. 102(b) as being anticipated by Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) is maintained.

The response filed 6/26/08 states that claims 14 and 24 each recite that the antibody fragment is a Fab or Fab' fragment, and that there are at least two effector molecules. Applicant states that pg. 23, lines 4-5 of Hesi et al teach that two polymer molecules can be attached when the fragment is F(ab')2, and at lines 9-11 that only one polymer molecules is attached when the fragment is Fab. Fab' or Fab'-SH. Applicant points to pg. 24, line 24-pg. 25, line 32 of Hesi et al, wherein the fragment is F(ab')2 and there are two polymers attached and pg. 25, line 33-pg. 28, line 4 wherein the fragment is selected from Fab, Fab', or Fab'-SH and there is only one polymer attached.

Applicant reiterates that Hesi et al does not teach the claimed structure wherein the fragment is a Fab or Fab' and has two effector molecules attached. Applicants' arguments have been fully considered but are not found persuasive. While Hesi et al does teach certain embodiments wherein the fragment is a F(ab')2 comprising two polymer molecules attached and Fab, Fab', or Fab'-SH wherein only one polymer molecule is attached, Hesi et al also teach additional embodiments wherein the fragment is a Fab, Fab' or Fab'-SH and wherein the conjugate contains no more than about 10 polymer molecules, or no more than 5 polymer molecules, or no more than about 4 polymer molecules, or no more than about 3 polymer molecules, or no more than about 2 polymer molecules, or no more than about 1 polymer molecule (e.g., see at least pg. 23, line 15-pg. 24, line 23, pp. 28-30, pg. 30, lines 30-36). Thus, while Hesi et al does teach F(ab')2 fragments comprising two polymer molecules attached and Fab, Fab', or Fab'-SH wherein only one polymer molecule is attached, Hesi also clearly teaches Fab, Fab' or Fab'-SH conjugated to at least two or more PEG molecules, i.e., the antibody is attached to 10 or fewer PEG molecules, attached to about 5 or fewer PEG molecules, attached to about 4 or fewer PEG molecules, attached to about 3 or fewer PEG molecules (e.g., pp. 28-29) as well as Hesi teaching that no more than about 10 polymer molecules, or no more than 5 polymer molecules, or no more than about 4 polymer molecules, or no more than about 3 polymer molecules, which provides significant overlap with the presently recited range of two or more effector molecules and as such Hesi et al provide "sufficient specificity" for anticipation of the claimed range of two or more effector molecules.

Thus, Hesi et al anticipate the claims and the rejection is maintained.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. The rejection of claims 24-29 under 35 U.S.C. 103(a) as being unpatentable over Singh et al (Analytical Biochemistry, 304(2):147-156, May 15, 2002) in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) and Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06) is maintained.

The response filed 6/26/08 states that one skilled in the art would not have attempted to attached PEG (or a derivative) to the interchain cysteines of a Fab or Fab' fragment because of the risk that the PEG would draw water away from the antibody fragment, creating destabilizing effect on the fragment that would force the heavy and light chains apart. Applicant states that the inventors discovered that, surprisingly, and contrary to prior perceptions in the art, an antibody fragment can be provided with PEG effector molecules attached to interchain cysteines, and the heavy and light chains remain associated with each other, such that the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in

which the interchain disulphide bond is present. Applicants' arguments have been fully considered but are not found persuasive. Applicants' arguments questioning the operability of the prior art, i.e., that PEGylation of the interchain cysteines would destabilize the antibody fragment and force the heavy and light chains apart, and applicants' allegations of the surprising and unexpected discovery that an antibody fragment can be provided with PEG effector molecules attached to interchain cysteines, and the heavy and light chains remain associated with each other, such that the PEGylated antibody Fab' fragment has equivalent antigen binding and *in vivo* activity compared to PEGylated Fab' fragments in which the interchain disulphide bond is present are acknowledged, however, applicant is reminded that the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). See MPEP 716.01(c).

Applicant also argues that Singh et al only describes the attachment of small molecules such as biotin to a whole antibody, not larger molecules such as PEG and Hesi teaches fragments in which one of the interchain cysteines has been substituted with serine, and no more than one polymer is attached to the fragment, the attachment being at the remaining interchain cysteine, however, claim 24 requires that an effector molecule is attached to both interchain cysteines. Applicant states that Humphreys teaches antibody fragments in which both interchain cysteines have been replaced with

serines and Humphreys makes no mention of fragments in which both the interchain cysteines were retained and have effector molecules attached. Applicants' arguments have been fully considered but are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further, in response to applicants' arguments that Singh et al is limited to the attachment of small effector molecules and Hesi only teaches the attachment of one polymer wherein attachment is at the interchain cysteine that is not substituted and that Humphreys discloses the replacement of both interchain cysteines with serine, applicant is reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures."). The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 USPQ 545 (CCPA 1969). In this case, the teachings of Hesi et al have been discussed supra and the teachings of Hesi et al are not limited to the attachment of one polymer wherein attachment is at the interchain cysteine that is not substituted as suggested by applicant. It is reiterated that Singh et al teach a rapid method for labeling antibodies comprising selenol-catalyzed reduction of interchain disulfides to generate thiol groups that are then labeled, wherein the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous

incorporation of labeled groups and this reduced disulfide labeling method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity and Hesi et al teach anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments for the treatment of inflammatory disorders wherein the antibody fragments are conjugated to two or more PEG molecules, i.e., the antibody is attached to 10 or fewer PEG molecules, attached to about 5 or fewer PEG molecules, attached to about 4 or fewer PEG molecules, attached to about 3 or fewer PEG molecules (e.g., pp. 28-29) and Humphreys teach Fab' hinge region peptides (i.e., SEQ ID Nos:1-3) that efficiently generates dimer (e.g., di-Fab), and the modified hinge peptides can be reduced to expose reactive thiols to which one, two, three or more effector molecules, including PEG may be attached. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising the cysteine containing hinge peptides of SEQ ID Nos:1-3 as taught by Humphreys and reduced using the selenol-catalyzed reduction of interchain disulfides to expose reactive thiols to which PEG molecules are attached since selenol-catalyzed reduction of interchain disulfides provides a rapid method in which the reduction and labeling steps are carried out in one vessel, results in quantitative and more predictable homologous incorporation of labeled groups and the method is superior to amino-group labeling methods because it is not inhibited by the presence of amines in solution and does not decrease antibody affinity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Further, one of ordinary skill in the art would have had a reasonable expectation of success in making the above modifications because Singh et al provides evidence that reduction of interchain disulfide bonds of an antibody does not result in a significant decrease in affinity or stability and selenol-catalyzed reduction of disulfide bonds in Fab fragments has been performed previously (Singh et al, pg. 148 1st col.). Applicant is reminded that obviousness does not require

absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 Fab, Fab', Fab-SH and F(ab')2 fragments comprising a cysteine modified hinge region of SEQ ID Nos:1-3 and PEGylated according to the selenol-catalyzed reduction of disulfides as taught by Singh et al for therapeutic benefit of inflammatory disorders in view of Singh et al and Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. The rejection of claims 4, 14-15, 17-19, 41 and 43 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7 and 10 of U.S. Patent No. 6,642,356 B1 in view of Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) is maintained.

The response filed 6/26/08 does not appear to address this rejection and as such the rejection is maintained for reasons already of record as set forth in the previous Office Action.

Applicant is reminded that the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned U.S. Patent No. 6,642,356 B1, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

22. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hesi et al (WO 98/37200, 8/27/1998, IDS reference 41 filed 10/20/06) in view of Humphreys D. P. (WO 99/15549, 4/1/1999, IDS reference 42 filed 10/20/06).

Hesi et al have been described supra. Hesi et al do not specifically teach wherein the hinge region comprises any one of the sequences of SEQ ID NO: 1 or 2. This deficiency is made up for in the teachings of Humphreys.

Humphreys teach Fab' hinge region peptides that efficiently generates dimers (e.g., di-Fab'), which are highly resistant to chemical reduction *in vivo* and the hinge peptides are well tolerated in *E.coli* and are non-immunogenic and the hinge region peptides of Humphreys are identical to the hinge regions of SEQ ID Nos:1-3 (see entire document, particularly pp. 2 and Table II).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced PEGylated anti-IL-8 di-Fab' fragments modified by replacement of either interchain cysteine with serine and comprising the hinge peptides taught by Humphreys for therapeutic benefit of inflammatory disorders.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to have produced anti-IL-8 di-Fab' fragments modified by replacement of either interchain cysteine with serine and comprising the hinge peptides taught by Humphreys for therapeutic benefit of inflammatory disorders in view of Hesi et al and Humphreys because Hesi et al teach PEGylated anti-IL-8 Fab' fragments for the treatment of inflammatory disorders wherein the disulfide bridge linking the heavy and light chains is avoided by substituting the cysteine residue of the heavy or light chain with serine and Humphreys teach Fab' hinge region peptides that efficiently generates dimers (e.g., di-Fab), which are highly resistant to chemical reduction *in vivo* and the hinge peptides are well tolerated in *E.coli* and are non-immunogenic and the hinge region peptides of Humphreys are identical to the hinge regions of SEQ ID Nos:1-3. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to use the hinge peptides of Humphreys in the PEGylated anti-IL-8 Fab' fragments of Hesi et al for efficient generation of nonimmunogenic di-Fab' fragments in *E.coli* that are resistant to chemical reduction *in vivo*. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Thus, the replacement of the

interchain cysteine of the CH1 with a serine and the use of the hinge peptide of SEQ ID NO:1 or SEQ ID NO:2 according to the teachings of Hesi et al and Humphreys et al (supra) would necessarily result in anti-IL-8 Fab' fragment comprising the interchain cysteine of the CL capable of forming a disulfide bond with a cysteine in the hinge region. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of obviousness has been established. *In re Best,* 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada,* 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman,* 596 F.2d 1019, 201 USPQ 658 (CCPA 1979).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced anti-IL-8 di-Fab' fragments modified by replacement of either interchain cysteine with serine and comprising the hinge peptides of Humphreys for therapeutic benefit of inflammatory disorders in view of Hesi et al and Humphreys.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Claim Objections

23. Claim 41 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 41 does not further limit base claim 14. Claim 41 recites wherein each effector molecule is PEG or a derivative thereof and base claim 14 has been amended to recite wherein each of the effector molecules is PEG or a derivative thereof. Thus, dependent claim 41 merely restates a

limitation presented in the base claim and as such does not add a limitation that is further limiting. The fourth paragraph of 35 U.S.C. 112, states that "a claim in a dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers" and requires the dependent claim to further limit the subject matter claimed.

Claim Rejections - 35 USC § 112

24. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

25. Claims 14-15, 17-20, 24-29, 41 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 18 is indefinite in the recitation "in which one of said effector molecules is attached to each cysteine in the hinge" as the exact meaning of the phrase cannot be determined. While one of the effector molecules can be attached to a single cysteine on the hinge region, it is unclear what is contemplated by one effector molecule attached to each cysteine in the hinge region. Is the one effector molecule crosslinked to multiple cysteines in the hinge region, does the hinge region only contain one cysteine, are there multiple effector molecules, or is some other meaning contemplated by the phrase. As written, one skilled in the art would not be reasonably apprised of the metes and bounds of the claim.

b. Claims 14-15, 17-20, 24-29, 41 and 43 are indefinite in the recitation "derivative thereof" in claims 14, 24 and 41 as the exact meaning of the word is not known. The term "derivative" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this term is the absence of an ascertainable meaning for said term. Since it is unclear the nature, direction and extent that the PEG molecules are to be derivatized to yield the class of derivatives referred to in the claims, there is no way

for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said term. In absence of a defined art recognized meaning for the term and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

26. Claims 5-7 are free of the prior art.

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643